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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 39750-0002DV1

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on August 25, 2005

Signature C. Rogers

Typed or printed name C. Rogers

Application Number	Filed
09/981,547	October 17, 2001

First Named Inventor: Wells, et al.

Art Unit	Examiner
1639	Epperson, Jon D.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 33,055
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

GINGER R. DREGER, ESQ.
Typed or printed name

650/324-7000
Telephone number

August 25, 2005
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Wells, et al.	Docket No.:	39750-0002DV1
Serial No.:	09/981,547	Group Art Unit:	1639
Filing Date:	October 17, 2001	Examiner:	Epperson, Jon D.

For: **METHODS FOR RAPIDLY IDENTIFYING SMALL ORGANIC MOLECULE LIGANDS FOR BINDING TO BIOLOGICAL TARGET MOLECULES**

MS: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Remarks/Arguments

Claims 58, 59, 61-66, and 81-96 are pending in this application. Claims 62-64, 66, 90-92 and 94 have been withdrawn from consideration as being directed to non-elected subject matter. Claims 58, 59, 61, 65, 81-89, 93, 95 and 96 stand rejected under 35 U.S.C. 103(a) as allegedly being obvious over Kim et al. (WO 98/11436) and Siuzdak, G. (Mass Spectrometry for Biotechnology, New York: Academic Press 1996, pages 199-126), and Jindal et al. (WO 97/01755).

The Invention

The invention is directed to a new strategy, called "tethering," for site-directed ligand discovery.

As claimed in claim 58, the invention is a method for identifying a non-oligomeric organic compound that has the greatest relative affinity for a target protein from a library of non-oligomeric organic compounds, less than 2000 daltons in size, that are capable of binding covalently to a chemically reactive group on the target protein to form a target protein-compound conjugate. The target protein and the library are contacted with each other in a mixture, and once a target protein-compound conjugate is formed, the mixture is analyzed by mass spectrometry. Using mass spectrometry, (1) the target protein-compound conjugate is detected, (2) the identity of the non-oligomeric organic compound present in the conjugate is determined, and (3) the compound is identified as having the greatest relative affinity for the target protein from the compounds present in the library analyzed. Accordingly, the method results in the identification of a novel ligand for the target protein.

The second independent claim, claim 85, claims a competition assay. In this assay, a mixture of a target protein, a reducing agent and at least two compounds that are less than 2000 daltons in size and are capable of forming a disulfide bond with the target protein, are contacted, the mixture is analyzed by mass spectrometry, and the most abundant target protein-compound conjugate formed is detected.

The Rejection

In simple terms, the rejection, which has been repeated in multiple Office Actions, is based on the premise that Kim et al. teaches all elements of independent claims 58 and 86, with the exception of using mass spectrometry to detect the target protein-compound conjugate, which, in turn, is said to be disclosed in Siuzdak. In the most recent, non-final Office Action, mailed on May 25, 2005 (hereinafter referred to as the "pending Office Action"), Jindal et al. is additionally cited and the Examiner states that the teaching missing from Kim et al. is supplied by "the combined references of Siuzdak and Jindal et al." (pending Office Action, page 7). In particular, Siuzdak is combined with Kim et al. to show that electrospray mass spectrometry can be used to study both non-covalent and covalent antibody-antigen interactions, including fragmentation techniques like MS^2 and MS^3 (see the passage bridging page 7 and 8 of the pending Office Action). Jindal et al. is combined with Kim et al. as allegedly showing that mass spectrometry can be applied to combinatorial libraries of targets and/or ligands for screening purposes. (See, page 8, lines 2-9 of the pending Office Action, which erroneously refers to the combination of Siuzdak et al. and Kim et al., but clearly means Jindal et al. and Kim et al.)

The Siuzdak Declaration

In order to rebut the Examiner's reading of Siuzdak, with a Preliminary Communication filed on February 28, 2005 concurrently with the filing of a Request for Continued Examination, Applicants submitted a Declaration of Gary Siuzdak, Ph.D., the author of the book, Chapter 6 of which has been cited by the Examiner as "Siuzdak."

According to paragraphs 3 and 4, Dr. Siuzdak disagrees with the Examiner's conclusion that his statement that "[e]lectrospray ionization mass spectrometry has also demonstrated its potential . . . for observing covalent protein-bound intermediates in an antibody-catalyzed reaction" would have motivated one skilled in the art to identify a novel ligand by the mass spectrometry detection of a covalently bound protein-ligand conjugate in a mixture.

In paragraph 6, Dr. Siuzdak explains that "[w]hile electrospray ionization mass spectrometry is well suited to study enzymatic mechanisms where all of the participants are known, its use to analyze mixtures of unknown components is limited." One reason for this is that "heterogeneous compounds can produce complicated spectra that can be difficult or impossible to interpret." Another obstacle is that "heterogeneous mixtures tend to reduce the sensitivity of electrospray ionization mass spectrometry." Dr. Siuzdak adds that "these obstacles are shared by other techniques of mass spectrometry."

In view of the foregoing explanation, in paragraph 7 Dr. Siuzdak states: "I do not believe that a person skilled in the art would have assumed that the mass spectrometry techniques to study enzymatic mechanisms would have been applicable to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected."

The Examiner's Dismissal of the Siuzdak Declaration

In the pending Office Action, the Examiner states that the Siuzdak Declaration is not found persuasive for the following reasons:

(1) "Although Dr. Gary **Siuzdak is unquestionably an expert in the field of mass spectrometry, his position in this particular case does not seem to be supported by the art.**" (Page 12, last paragraph, emphasis added.)

(2) In addressing Dr. Siuzdak's conclusion that a person skilled in the art the time the present invention was made would not have assumed that the mass spectrometry techniques used to study enzymatic mechanisms would have been applicable to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected, the Examiner cites Jindal et al., as allegedly showing that "mass spectrometry was 'routinely' applied to 'unknown' targets and/or ligand including 'complicated' mixtures like combinatorial libraries."

(3) Finally, the Examiner "reiterates that **the Siuzdak reference is only one of potentially hundreds if not thousands of references**" that support his position. (Emphasis added.) The Examiner further refers to the Advisory Action of December 20, 2004, presumably to point at the documents cited under the heading "References Illustrative of the State of Prior Art," although this is not entirely clear from the pending Office Action.

The Examiner's dismissal of the conclusions of the Siuzdak Declaration is improper

It is well established that Office personnel must accept an opinion from a qualified expert based on relevant facts. It is improper to disregard such opinion solely because the Examiner disagrees with its conclusions. In the present case, Applicants submitted a Declaration by the very author of the book chapter cited in support of the pending obviousness rejection. While the Examiner has acknowledged that the author of the Declaration, Dr. Siuzdak is unquestionably an expert in the field, his conclusions were dismissed, since they were allegedly contradicted by Jindal et al. and by "potentially hundreds if not thousands of references," none of which is cited or applied against the claims pending. As it will be shown below, Jindal et al. does not contradict the opinion of Dr. Siuzdak. Indeed, it would be surprising if the Examiner could cite even one reference (let alone hundreds or thousands of references), which could validly contradict a renown scientist's explanation of and conclusions drawn from his own work.

There is no motivation to combine Kim et al. and Siuzdak

The requirement that an examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. The motivation to modify a reference can come from (1) the nature of the problem to be solved, (2) the teachings of the prior art itself,

or (3) the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d 1350; 47 USPQ2d 1453 (Fed. Cir. 1998).

The motivation to combine Kim et al. and Siuzdak does not derive from the nature of the problem to be solved. In the present case, the relevant problem to be solved is (1) the detection of the most abundant target protein-compound conjugate in a mixture of target protein-compound conjugates, and the determination of the identity of the compound present in the most abundant conjugate, which will be the compound having the greatest relative affinity for the target protein of the compounds present in the mixture assayed (claim 58), or (2) to detect the most abundant protein-compound conjugate formed in a mixture containing the target protein, at least two compounds that are capable of forming a conjugate with the target protein through disulfide bond formation and a reducing agent (claim 86). The Siuzdak Declaration clearly establishes that mass spectrometry would not have been the method of choice for either case. The Examiner's citation of Jindal et al. does not change this conclusion, since it does not contradict the conclusion of the Siuzdak Declaration. Jindal et al. disclose a complex chromatography-based screening method for identifying a ligand for a target of interest in a peptide library. The mixture screened contains three types of peptides; those that i) have no affinity to any protein, ii) bind to a large number of proteins, or iii) show affinity to a specific target protein. The screening system of Jindal et al. differentiates among these various peptides using a series of chromatographic separation steps, each based on an different physico-chemical characteristic, ultimately leading to the separation of one or more ligands for the target protein, which are then identified by any method know in the art suitable for detection, including mass spectrometry and subsequent peptide sequencing. This is in contrast to the present invention, which does not involve such separation steps, and where a complex mixture of target protein-ligand conjugates and optionally ligand candidates is analyzed by mass spectrometry, allowing the determination of the identity of a particular ligand from among the conjugates and ligand candidates present, which typically tend to have very similar molecular weights. Since neither Siuzdak et al. nor Jindal et al. address the problem addressed by the present inventors, the motivation to combine does not derive from the nature of the problem to be solved.

The motivation to combine Kim et al. and Siuzdak does not derive from the teachings of the prior art either. The only detection method specifically disclosed in Kim et al. is detection using antibodies (page 21, second sentence of first full paragraph). Mass spectrometry is nowhere suggested. Siuzdak et al. teach the use of electrospray ionization mass spectrometry for studying noncovalent binding between an antibody and its antigen, both known entities. Dr. Siuzdak, author of the cited chapter, unambiguously states his opinion that from this teaching one would not have assumed that a similar approach would work "to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected." Jindal et al. does not change this conclusion since it does not and cannot supply the teaching missing from Siuzdak et al. Nor does Jindal et al. contradict the statements in the Siuzdak Declaration, since it suggests the use of mass spectrometry in a context that significantly differs both from the methods of the present application and from the much simpler methods disclosed in the Siuzdak reference.

The motivation to combine Kim et al. and Siudak does not derive from the knowledge or persons of ordinary skill in the art. Dr. Siuzdak, an unquestionable person skilled in the art, can't see the motivation to combine. Accordingly, his Declaration creates a strong presumption that such motivation does not exist. The Examiner's attempt to discredit Dr. Siuzdak's statement by citing a reference using mass spectrometry in a method that significantly differs from the method of the present invention is not sufficient to overcome this strong presumption.

In conclusion, it is submitted that the Examiner failed to establish a *prima facie* case of obviousness, and the present rejection should be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 **(Attorney Docket No.: 39750-0002DV1)**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 25, 2005

Ginger R. Dreger, Esq.
Reg. No. 33,055

HELLER EHRMAN, LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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